

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



Rec'd PCT/PTO 18 FEB 2005



(43) International Publication Date  
18 March 2004 (18.03.2004)

PCT

(10) International Publication Number  
**WO 2004/022105 A3**

- (51) International Patent Classification<sup>7</sup>: **A61K 51/04**, 51/12, C07F 1/08, 13/00, 15/00
- (21) International Application Number: **PCT/US2003/027665**
- (22) International Filing Date:  
2 September 2003 (02.09.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
02078743.8 3 September 2002 (03.09.2002) EP
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): **MALLINCKRODT INC.** [US/US]; 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **ALBERTO, Roger** [CH/CH]; St. Georgenstrasse 54, CH-8400 Winterthur (CH). **MUNDWILER, Stefan** [CH/CH]; Colmarerstrasse 59, CH-4055 Basel (CH).
- (74) Agents: **CHEATHAM, Tim, A.** et al.; 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).
- Published:  
— with international search report  
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report:  
22 April 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: PREPARATION OF M(CO)<sub>3</sub>-COMPLEXES BY SOLID PHASE TECHNIQUES VIA METAL ASSISTED CLEAVAGE FROM THE SOLID SUPPORT

(57) Abstract: The present invention relates to a process for generating a water soluble metal complexed agent, comprising contacting a solid phase bound organic conjugate represented by the formula I with  $[M(H_2O)_3(CO)_3]^{n+}$ , under suitable conditions to cause the formation of a coordinate bond between  $[M(H_2O)_3(CO)_3]^{n+}$  and the tertiary amine nitrogen atom of the solid phase bound organic conjugate and thereby the release of the metal complexed agent thus formed from the support. The invention further relates to the conjugate of formula (I) and to a kit for performing the process.

WO 2004/022105 A3

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/27665

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61K51/04 A61K51/12 C07F1/08 C07F13/00 C07F15/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K C07F		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHIBLI R ET AL: "Steps toward high specific activity labelling of biomolecules for therapeutic application: preparation of precursor "188!Re(H <sub>2</sub> O) <sub>3</sub> (CO) <sub>3</sub> !+ and synthesis of tailor-made bifunctional ligand systems" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 13, no. 4, 7 July 2002 (2002-07-07), pages 750-756, XP002218738 ISSN: 1043-1802	19
Y	the whole document ----- -/--	1-18, 20-24
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family		
Date of the actual completion of the international search  10 December 2003		Date of mailing of the international search report  11/02/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  Elliott, A

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/27665

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LA BELLA R ET AL: "A '99m!Tc(I)-postlabelled high affinity bombesin analogue as a potential tumor imaging agent" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 13, no. 3, 15 May 2002 (2002-05-15), pages 599-604, XP002218739 ISSN: 1043-1802	19
Y	figure 1	1-18, 20-24
X	--- JANG B-S ET AL: "Synthesis of '99m!Tc-tricarbonyl precursors for labelling of bioactive molecules" JOURNAL OF THE KOREAN NUCLEAR SOCIETY, vol. 34, no. 2, April 2002 (2002-04), pages 146-153, XP001117823 ISSN: 0372-7327	19
Y	the whole document	1-18, 20-24
X	--- WO 01 89586 A (MALLINCKRODT INC) 29 November 2001 (2001-11-29)	19
Y	claims 8-17	1-18, 20-24
X	--- LANGER M ET AL: "'99m!Tc-labelled neuropeptide Y analogues as potential tumour imaging agents" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 12, November 2001 (2001-11), pages 1028-1034, XP001059452 ISSN: 1043-1802	19
Y	figure 1	1-18, 20-24
X	--- SEIFERT S ET AL: "REACTIVITY OF TECHNETIUM(I) THIOETHER CARBONYL COMPLEXES TOWARDS HISTIDINE-AN EXAFS STUDY IN SOLUTION" INORGANICA CHIMICA ACTA, LAUSANNE, CH, vol. 322, 8 October 2001 (2001-10-08), pages 79-86, XP001074703 ISSN: 0020-1693	19
Y	figures 1,3	1-18, 20-24
	--- -/--	

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/27665

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CORREIA J D G ET AL: "Re Tricarbonyl Complexes with Ligands Containing P,N,N and P,N,O Donor Atom Sets: Synthesis and Structural Characterisation" INORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 40, no. 20, 24 September 2001 (2001-09-24), pages 5147-65151, XP002218740 ISSN: 0020-1669	19
Y	* Scheme 1 *	1-18, 20-24
X	--- PETRIG J ET AL: "Derivatisation of glucose and 2-deoxyglucose for transition metal complexation: substitution reactions with organometallic <sup>99m</sup> Tc and Re precursors and fundamental NMR investigations" CHEMISTRY - A EUROPEAN JOURNAL, WILEY-VCH, WEILHEIM, DE, vol. 7, no. 9, 4 May 2001 (2001-05-04), pages 1866-1873, XP002218741 ISSN: 0947-6539	19
Y	* Scheme 3 *	1-18, 20-24
X	--- FALLER J W ET AL: "The synthesis of new complexes of rhenium(I) with heterotridentate 'P,N,O' ligands" JOURNAL OF ORGANOMETALLIC CHEMISTRY, ELSEVIER-SEQUOIA S.A. LAUSANNE, CH, vol. 626, no. 1-2, 30 April 2001 (2001-04-30), pages 181-185, XP004235661 ISSN: 0022-328X	19
Y	* Scheme 1 *	1-18, 20-24
X	WO 01 00637 A (MALLINCKRODT INC) 4 January 2001 (2001-01-04)	19
Y	claims 15,16	1-18, 20-24
X	--- EP 1 013 642 A (SCHERING AG) 28 June 2000 (2000-06-28)	19
Y	claims; examples 3C,4B,5B,9B	1-18, 20-24
	--- -/--	

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/27665

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHIBLI R ET AL: "Influence of the denticity of ligand systems on the in vitro and in vivo behaviour of <sup>99m</sup> Tc(I)-tricarbonyl complexes: a hint for the future functionalisation of biomolecules" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 11, no. 3, May 2000 (2000-05), pages 345-351, XP002218742 ISSN: 1043-1802	19
Y	* Scheme 1 *	1-18, 20-24
X	WO 98 48848 A (MALLINCKRODT MEDICAL INC) 5 November 1998 (1998-11-05)	19
Y	the whole document	1-18, 20-24
Y	POLLAK A ET AL: "A convenient method of preparing high specific activity technetium complexes using thiol-containing chelators absorbed on gold" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 121, no. 49, 15 December 1999 (1999-12-15), pages 11593-11594, XP002218743 ISSN: 0002-7863 cited in the application the whole document	1-18, 20-24
X	ALBERTO ET AL: "A Novel Organometallic Aqua Complex of Technetium for the Labeling of Biomolecules: Synthesis of <sup>99m</sup> Tc(OH <sub>2</sub> ) <sub>3</sub> (CO) <sub>3</sub> !+ from <sup>99m</sup> TcO <sub>4</sub> !- in Aqueous Solution and Its Reaction with a Bifunctional Ligand" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 120, no. 31, 12 August 1998 (1998-08-12), pages 7987-7988, XP002149527 ISSN: 0002-7863	19
Y	* Scheme 2 *	1-18, 20-24
	---	
	-/--	

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/27665

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STOR G J ET AL: "Spectroelectrochemical (IR, UV/Vis) determination of the reductive pathways for a series of 'Re(CO)3(alpha-diimine)L'!O/+ (L' = Halide, Otf-, THF, MeCN, n-PrCN, PPh3, P(OMe)3) complexes" ORGANOMETALLICS, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 14, no. 3, March 1995 (1995-03), pages 1115-1131, XP002218744 ISSN: 0276-7333	19
Y	the whole document	1-18, 20-24
X	ALBERTO R ET AL: "New organometallic technetium complexes in high and low oxidation states" RADIOCHIMICA ACTA, LONDON, GB, vol. 63, 1993, pages 153-161, XP002060831 * Compound 10 *	19
Y		1-18, 20-24
Y	DUNN-DUFAULT R ET AL: "A solid-phase technique for preparation of no-carrier-added technetium-99m radiopharmaceuticals: application to the streptavidin/biotin system" NUCLEAR MEDICINE AND BIOLOGY, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 27, no. 8, November 2000 (2000-11), pages 803-807, XP004228484 ISSN: 0969-8051 cited in the application the whole document	1-18, 20-24
Y	KHEHYONG N ET AL: "Preparation of Acid-labile Resins with Halide Linkers and their Utility in Solid Phase Organic Synthesis" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 38, no. 6, 10 February 1997 (1997-02-10), pages 973-976, XP004033909 ISSN: 0040-4039 cited in the application the whole document	1-18, 20-24
Y	US 5 789 555 A (POLLAK ALFRED) 4 August 1998 (1998-08-04) cited in the application the whole document	1-18, 20-24

-/-

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/27665

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VAN WIJNKOP M ET AL: "1,3-Dipolar cycloaddition reactions to the C=X-M fragment. 7. Reaction of Ru(CO) <sub>3</sub> (1-Pr-DAB) with dimethyl acetylenedicarboxylate. X-ray crystal structure of the protonated initial bicyclo[2.2.1] adduct" ORGANOMETALLICS, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 11, no. 11, November 1992 (1992-11), pages 3607-3617, XP002218745 ISSN: 0276-7333	19
Y	figures	1-18, 20-24
A	WO 01 25243 A (MALLINCKRODT INC) 12 April 2001 (2001-04-12) the whole document	1-24

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/27665

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0189586 A	29-11-2001	US 6359119 B1 EP 1283729 A2 WO 0189586 A2 US 2002147316 A1	19-03-2002 19-02-2003 29-11-2001 10-10-2002
WO 0100637 A	04-01-2001	AU 6488900 A CA 2377018 A1 CZ 20014603 A3 EP 1192166 A1 HU 0301779 A2 JP 2003503415 T WO 0100637 A1	31-01-2001 04-01-2001 13-11-2002 03-04-2002 28-08-2003 28-01-2003 04-01-2001
EP 1013642 A	28-06-2000	DE 19860289 A1 EP 1013642 A2 US 6488909 B1	29-06-2000 28-06-2000 03-12-2002
WO 9848848 A	05-11-1998	EP 0879606 A1 AT 211924 T AU 748213 B2 AU 7141398 A BR 9809409 A DE 69803205 D1 DE 69803205 T2 DK 1019095 T3 EP 1019095 A1 ES 2168751 T3 HU 0003255 A2 JP 2002512616 T NO 995160 A NZ 337303 A PL 336382 A1 PT 1019095 T WO 9848848 A1 US 6344178 B1	25-11-1998 15-02-2002 30-05-2002 24-11-1998 13-06-2000 21-02-2002 19-09-2002 06-05-2002 19-07-2000 16-06-2002 28-02-2001 23-04-2002 13-12-1999 22-12-2000 19-06-2000 31-07-2002 05-11-1998 05-02-2002
US 5789555 A	04-08-1998	AU 8137694 A EP 0730472 A1 JP 9505061 T	06-06-1995 11-09-1996 20-05-1997
WO 0125243 A	12-04-2001	AU 1134401 A CA 2385927 A1 CN 1377360 T CZ 20021118 A3 WO 0125243 A1 EP 1218385 A1 HU 0203138 A2 JP 2003511334 T	10-05-2001 12-04-2001 30-10-2002 16-04-2003 12-04-2001 03-07-2002 28-12-2002 25-03-2003